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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/706,659	11/12/2003	Joseph L. Witztum	1034123-000014	3280

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EXAMINER	
COOK, LISA V	

ART UNIT	PAPER NUMBER
1641	

NOTIFICATION DATE	DELIVERY MODE
01/29/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/706,659	WITZTUM ET AL.	
	Examiner	Art Unit	
	Lisa V. Cook	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2007 and 18 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/19/07 has been entered.

Amendment Entry

2. Applicants' response to the Final Office Action mailed October 16, 2006 (petition and response filed 6/18/07) is acknowledged. Claims 27 and 31 have been cancelled. New claims 33-40 have been added. Currently claims 33-40 are pending and under consideration.

3. Objections and/or rejections of record not reiterated herein have been withdrawn.

NEW GROUNDS OF REJECTIONS NECESSITATED BY AMENDMENT

Please note: The instant claims (33-40) are drawn to antibody (protein) configurations, however the structures are defined by nucleotide sequences that encode the proteins. Since a single nucleotide sequence can encode multiple protein sequences the actual structure that Applicant intends to claim is ambiguous.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 33-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claims 33-40 the antibody is vague and indefinite because the claims, merely identifies the antibody by function and nucleotide sequences. Because the antibody is a protein and various different proteins can be encoded by the *same* nucleotide sequence the intended antibody is not clear. It is suggested that the actual sequences comprising the antibody be recited in the claims in order to obviate this rejection. Please correct.

B. In claims 33-40, " fragment antibody and single chain fragment" is vague and indefinite because it is unclear as to what the terms will encompass. The claim do not sets forth an antibody structure or the necessary binding epitopes for binding specificity. Thus the antibody portions that would meet the claimed limitation have not been identified. Therefore the undefined fragments would are unclear. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 33-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification is not enabled for the claimed antibodies because the instant specification is not in compliance with the biological deposit rules.

Claims 33-40 are directed to antibodies having particular binding specificity (like IK17, comprising SEQ ID NO:1/SEQ ID NO:2, binding atherosclerotic plaques, binding OxLDL and binding MDA-LDL). However, the claimed antibodies have not been deposited under the provisions of the Budapest treaty. Furthermore, filling of an affidavit or declaration by Applicant or assignee or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this Application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required.

Without such a statement, it would be impossible for the skilled artisan to practice the invention of claims 33-40 because other clones made from the source material have no predictable reasonable expectation of success of being identical to the instantly claimed antibodies.

In the absence of any guidance other than to the use of the Mab IK17, one would not know or be able to predict what structure or modifications were important and the amount of experimentation required to determine same would be undue. Note that an enabling disclosure for the preparation and use of only a few analogs of a product does not enable all possible analogs where the characteristics of the analogs are unpredictable.

Accordingly, the art indicates that it would require undue experimentation to formulate and use a successful antibodies as recited in the instant invention without the prior demonstration of specific limitations that have not been recited. Amgen Inc. v. Chugai Pharmaceutical Co. Ltd. (18 USPQ 2d 1027 (CAFC 1991)).

6. Claims 33-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 33-40 are drawn to antibody fragments. The written description in this case does not set forth *any sequence* by which the claimed fragments can be determined, therefore the written description does not reasonably convey the claimed subject matter to one of ordinary skill in the art. Neither the specification nor the claims teach how to define or obtain binding fragments.

There is no guidance as to what the fragments are or how much modification can occur while maintaining product characteristics with respect to the instant invention. There is no guidance as to what fragments can or cannot be utilized for its intended purpose. The specification does not include structural examples of binding fragments, in fact no peptide sequence is included in the disclosure. Thus, the resulting binding fragments could result in any number of complexes not taught and enabled by the specification.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Without a sequence or examples of antibody fragments, the skilled artisan cannot envision the detailed structure of the binding fragments, thus conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. An adequate description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it.

The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of molecules falling within the scope of the claimed genus. Therefore the full breadth of the claims, reading on fragments of the claimed antibody does not meet the written description provision of 35 USC 112, first paragraph.

7. Claims 33-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining, whether a disclosure would require undue experimentation include 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of those in the art, and 8) the breadth of the claims.

In particular, claims 33-40 are drawn to any antibody having the binding specificity of the IK17 antibody, the antibody is encoded by nucleotide sequences comprising SEQ ID NO:1 and SEQ ID NO:2; the antibody is specific for oxidized low density lipoprotein and malondialdehyde low density lipoprotein, and having *in vivo* utility. However, the claimed antibody structures are defined by nucleotide sequences that encode the proteins. Since a single nucleotide sequence can encode multiple protein sequences the actual structure that Applicant intends to claim is ambiguous and has not been identified by the specification.

Further, it is not known how the monoclonal antibody having single binding specificity will bind both oxidized low-density lipoprotein and malondialdehyde low-density lipoprotein simultaneously. The claims and specification fail to provide the identity or structure of this antibody recognition site.

The specification does not provide evidence of a nucleic acid sequence, other than the sequence of SEQ ID NO: 1 and SEQ ID NO: 2 which are known in the art. From these known sequences primers are produced with the claimed inventive properties; however the specification does not state the identity to a deposited antibody, amino acid sequence, nucleic acid sequence, or any structural characteristics of any other antibody, amino acid sequence, or nucleic acid sequence that has the claimed characteristics.

Moreover, there is evidence that other sequences have not yet been identified therefore; applicants' vague description of an isolated nucleic acid sequence (primers from SEQ ID NO: 1 and SEQ ID NO: 2) has not been adequately described.

In view of the lack of evidence, it is apparent that Applicants were not in possession of the unlimited number of primers which may be produced from the known sequences of SEQ ID NO: 1 and SEQ ID NO: 2, at the time of filing the instant application. It is not clear that Applicant has identified a single antibody protein configuration that meets the claimed limitations.

The skilled artisan cannot envision the detailed structure of the infinite possible antibodies, amino acid sequences, or isolated nucleic acid sequences, thus conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. An adequate description requires more than a mere statement that it is part of the invention. The nucleic acid structure is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

The antibod y activity characteristics and tail domain requirements distinguish the antibody only by what it does, i.e., protein activity, which are purely functional distinctions. Even where there is an actual reduction to practice, which may demonstrate possession of an embodiment of an invention, it does not necessarily describe what the claimed invention is. The instant specification and claims describe an isolated monoclonal antibody by its protein function, however this description does not describe the claimed antibody itself. See also, *In The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), where the court held that a generic statement which defines a genus of a compound/seq.id/etc. by only their functional activity does not provide an adequate written description of the genus.

The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of molecules, usually defined by a sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description ...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Thus a skilled artisan cannot envision all the contemplated recognition sequence sites by the detailed chemical structure of the claimed antibody, therefore conception cannot be achieved until reduction to practice has occurred. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

Applicant does not provide guidance for the above noted monoclonal antibodies and provides no guidance as to what modifications or structure are important for the predictable function of the monospecific antibody. Very different structures may be found on antibodies with the same specificity. For example, very different V_H chains can combine with the same V_L chain to produce antibody binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_L sequences to produce antibodies with very similar properties.

These observations indicate that divergent variable region sequences, both in and out of complementarily determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. Conversely, similar structure may be found on antibodies having different specificities.

In the recent court decision of Noelle v. Lederman, 355 F.3d 1343 (Fed. Cir. 2004), claims which recite a genus of antibodies that bound to a mouse antigen were found to be unpatentable, because the corresponding human antigen had not been adequately characterized. This is the same issue currently at hand. The antibody antigen (protein structure) has not been identified in the disclosure.

In addition, the development of non-naturally occurring/synthetic bifunctional molecules (antibody variables – light and heavy chain) with binding characteristics of interest necessitates several conditions which have not been described in the instant specification. In one instance, the prior art discloses that the development of inhibitors which can bind by both an active site specific interaction to a primary binding site and by a structure nonspecific hydrophobic interaction to a second site (bifunctional or bispecific molecules) requires several parameters to produce the intended binding specificity. "Epitope binding of Cu-OxLDL and MDA-LDL".

These parameters include; a crystal structure of the enzyme with the bound primary inhibitor, there must be a relatively "open" active site, to permit access to the active site, and the linker must introduce few unfavorable enthalpic and entropic interactions into the bound state. See Jein et al., J Med Chem., 1994, 37, 2100-2105, especially scheme 1 and page 2103, 2nd column 2nd paragraph.

These parameters have not been addressed by the instant disclosure. Therefore one of skill in the art would not be able to predict the antibody molecules effects *in vivo*.

In other words, the bifunctional molecule must be evaluated in a host in order to determine efficacy or inhibition effects. See Kuduk et al. Bio & Med Chemistry Letters, 10, 2000, 1303-1306, in particular page 1305, 2nd column Conclusion, 2nd paragraph.

Further, the art teaches that successful *in vitro* bifunctional construct binding is not always indicative of the *in vivo* results exhibited by that same bifunctional molecule. For example, see Peipp and Valerius page 510 – Conclusion, wherein "Results from clinical trials (in vivo effective dosage) with bispecific antibodies are less encouraging". Peipp and Valerius, Biochemistry Society Transactions, 2002, Volume 30, part 4, pages 507-511.

Accordingly, the specification does not provide substantive evidence that the claimed bifunctional antibody molecules are capable of binding *in vivo*. This demonstration is required for the skilled artisan to be able to use the claimed bifunctional antibodies molecules for their intended purpose.

Without this demonstration, the skilled artisan would not be able to predict the outcome of the administration of the claimed bifunctional or bispecific non-naturally occurring antibody compositions. The ability to reasonably predict the capacity of a single non -naturally occurring bifunctional molecule to produce protein-protein interaction in vivo is problematic.

Unfortunately, the art is replete with instances where even well characterized compositions that induce an in vitro response fails to elicit *in vivo* utility. See Waldmann, Science, Vol.252, 21 June 1991, pages 1657-1662, in particular page 1657 – 2nd column, wherein antibodies binding therapy has proven elusive and only one monoclonal antibody has been licensed for clinical utility.

Accordingly, the art indicates that it would require undue experimentation to formulate and use a successful binding composition with out prior demonstration of efficacy.

The instant disclosure has not addressed the issues taught in the prior art as crucial to the discovery of a biopolymer marker.

The nature of the invention- the invention is directed to an unidentified antibody composition.

The state of the prior art- the prior art of record fails to disclose the particular antibody meeting the claimed limitations.

The predictability or lack thereof in the art- there is no predictability based on the instant specification that the antibody and its structure can be readily identified.

The amount of direction or guidance present- appropriate guidance is not provided by the specification for the claimed antibodies.

The presence or absence of working examples- working examples are not provided in the specification that identify and/or exemplify the claimed antibodies.

The quantity of experimentation necessary- it would require undue amount of experimentation for the skilled artisan to make and use the antibodies as claimed.

*The relative skill of those in the art-*the level of skill in the art is high.

The breadth of the claims- as recited, the instant claims are directed to antibodies comprising sequences encoded by SEQ ID NO:1 and SEQ ID NO:2, but does not teach the actual peptide sequence.

While it is not necessary to show working examples for every possible embodiment, there should be sufficient teachings in the specification that would suggest to the skilled artisan that the breadth of the claimed antibody is enabled. This is not the case in the instant specification.

In view of the teachings of In re Wands, 8 USPQ2d 1400, it has been determined that the level of experimentation required to enable the breadth of the claims is undue.

Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966). While every aspect of a generic claim does not have to be carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. Genetech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001. That requirement has not been met in this specification with respect to the biopolymer consisting of SEQ ID NO:4 diagnostic for Type II diabetes.

Therefore, in view of the insufficient guidance in the specification, extensive experimentation would be required to enable the claims and to practice the invention as claimed.

8. For reasons aforementioned, no claims are allowed.

Remarks

9. Prior art made of record and not relied upon is considered pertinent to the applicant's disclosure:

A. Selley et al. (WO 94/23302) teach an immunological ELISA assay-employing antibodies to measure oxidatively modified human low-density lipoproteins in plasma samples.

B. Holvoet et al. (Journal of Clinical Investigation, Vol.95., No.6., 1 June 1995, pages 2611-2619) disclose a method for detecting MDA-modified LDL. A monoclonal antibody (mAb-1H11) which to bind with MDA-modified LDL ($ka=10^9\ M^{-1}$) and to a much lesser extent with OxLDL (page 2613, column 2, paragraph 1) is described in an immunoassay format.

10. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The Group 1641 – Central Fax number is (571) 273-8300, which is able to receive transmissions 24 hours/day, 7 days/week. In the event Applicant would like to fax an unofficial communication, the Examiner should be contacted for the appropriate Right Fax number.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday - Friday from 7:00 AM - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (571) 272-0823.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group TC 1600 whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see httpr//pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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